



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 9/00	A1	(11) International Publication Number: WO 98/43611 (43) International Publication Date: 8 October 1998 (08.10.98)
(21) International Application Number: PCT/US98/05138 (22) International Filing Date: 17 March 1998 (17.03.98) (30) Priority Data: 60/042,196 31 March 1997 (31.03.97) US (71) Applicant (for all designated States except US): ALZA CORPORATION [US/US]; 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-08802 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): ROORDA, Wouter, E. [NL/US]; 7596 Birkdale Drive, Newark, CA 94560 (US). DIONNE, Keith, E. [US/US]; 4 Hancock Park, Cambridge, MA 01239 (US). BROWN, James, E. [US/US]; 126 Blueberry Hill Drive, Los Gatos, CA 95032 (US). WRIGHT, Jeremy, C. [US/US]; 631 Cuesta Drive, Los Altos, CA 94024 (US). DAVIS, Craig, R. [US/US]; 5237 Orkney Court, Newark, CA 94560 (US). PRESTRELSKI, Steven, J. [US/US]; 1971 West Middlefield Road #5, Mountain View, CA 94043 (US). TZANNIS, Stelios, T. [GR/US]; 1901 Rock Street, Mountain View, CA 94043 (US).		(74) Agents: CLARKE, Pauline, A. et al.; Alza Corporation, 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: DIFFUSIONAL IMPLANTABLE DELIVERY SYSTEM		
(57) Abstract <p>A sustained release delivery system for delivering a beneficial agent is provided. The system includes a reservoir comprising the beneficial agent and a capillary channel in communication with the reservoir and the exterior of the system for delivering the beneficial agent from the system. The capillary channel has a cross-sectional area and a length selected to deliver the beneficial agent at a predetermined rate. The system may further include an outer surface that is impermeable and non-porous during delivery of the beneficial agent. The beneficial agent may be formulated in a glassy sugar matrix.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Larvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav	TM	Turkmenistan
BF	Burkina Faso	GR	Greece		Republic of Macedonia	TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's	NZ	New Zealand		
CM	Cameroon		Republic of Korea	PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

DIFFUSIONAL IMPLANTABLE DELIVERY SYSTEM

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention generally relates to a sustained release beneficial agent delivery system. More particularly, the invention relates to a sustained release beneficial agent delivery system having a capillary channel for controlling the rate of release of the beneficial agent by diffusion.

2. Description of the Related Art

Various dispensing systems for the delivery of active agents are known in the art. These systems generally deliver the active agent by diffusion from an enclosed capsule or from a multi-structured device having a wall formed of a polymer permeable to water and/or to the agent into a selected environment. See, e.g., U.S. Patent Nos. 4,135,514; 3,760,806; 3,760,984; and 3,995,631. However, there is a large category of agents that cannot be readily delivered by such prior art systems because of at least one feature inherent in the devices which adversely affects the rate of release of the agent from the device. For example, many agents cannot be effectively delivered from a diffusion controlled delivery system because their permeation rate through the rate controlling material of the system is too small to produce a useful effect.

There is an additional class of active agents that also cannot be satisfactorily delivered by diffusional devices because of a particular chemical characteristic of the agent. This additional class includes salts that, because of their ionic character, will not readily diffuse through polymeric membranes. This class also includes unstable polar compounds that cannot be formulated into a satisfactory composition suitable for storage and delivery from such prior art systems.

In view of the above-mentioned disadvantages of prior art diffusional delivery systems and devices, there is a need in the art for a system that is capable of providing sustained delivery of beneficial agents, particularly, of beneficial agents that do not readily permeate through polymeric membranes.

SUMMARY OF THE INVENTION

1
2 It is, therefore, an object of the present invention to provide a diffusional
3 delivery system suitable for the controlled and sustained release of a beneficial agent.

4 In one embodiment, the system includes a reservoir comprising a beneficial
5 agent and a capillary channel in communication with the reservoir and the exterior of
6 the device for delivering the beneficial agent from the device. The capillary channel
7 has a cross-sectional area and a length selected to deliver the beneficial agent at a
8 predetermined rate. The system further includes an outer surface that is impermeable
9 and non-porous during delivery of the beneficial agent.

10 In another embodiment, the system includes a reservoir comprising a
11 beneficial agent formulated in a glassy sugar matrix and a capillary channel in
12 communication with the reservoir and the exterior of the device for delivering the
13 beneficial agent from the device. The capillary channel has a cross-sectional area
14 and a length selected to deliver the beneficial agent at a predetermined rate.

15 Another object of the present invention is to provide a method for delivering
16 a beneficial agent at a predetermined rate using the sustained release delivery system
17 according to the present invention. The method includes positioning the sustained
18 release delivery system at a location in need of the beneficial agent or where release
19 of the beneficial agent is desired, and allowing the beneficial agent to pass through
20 the capillary channel of the delivery system to obtain a desired effect.

21 Another object of the present invention is to provide a method of preparing a
22 sustained release delivery system for delivering a beneficial agent at a predetermined
23 rate. The method includes the steps of providing a reservoir having an outer surface
24 that is impermeable and non-porous during delivery of the beneficial agent, filling
25 the reservoir with the beneficial agent, and providing the reservoir with a diffusion
26 controller. The diffusion controller comprises a capillary channel having a cross-
27 sectional area and a length selected to provide the predetermined rate.

28 Another object of the present invention is to provide a method of preparing a
29 sustained release delivery system for delivering a beneficial agent formulated in a
30 glassy sugar matrix at a predetermined rate. The method includes the steps of
31 providing a reservoir, providing a beneficial agent formulated in a glassy sugar matrix

1 in the reservoir, and providing the reservoir with a diffusion controller. The diffusion
2 controller comprises a capillary channel having a cross-sectional area and a length
3 selected to provide the predetermined rate.

4 Other objects, advantages, features, and aspects of the invention will become
5 readily apparent in view of the following detailed description and the appended claims
6 and drawings.

7 8 BRIEF DESCRIPTION OF THE DRAWINGS

9 The drawings, which are not drawn to scale, are provided to illustrate various
10 embodiments of the invention. The drawings are as follows:

11 FIG. 1 is an enlarged view of one embodiment of the sustained release
12 beneficial agent delivery system showing a beneficial agent reservoir and a long,
13 narrow capillary channel;

14 FIG. 2 is an enlarged view of another embodiment of the sustained release
15 beneficial agent delivery system showing a beneficial agent reservoir, a long, narrow
16 capillary channel, and an implant attachment;

17 FIG. 3 is an enlarged view of the sustained release delivery system prepared
18 according to the example herein; and

19 FIG. 4 is a graph showing the release rates as a function of time of the delivery
20 systems prepared according to the example herein.

21 22 DESCRIPTION OF THE PREFERRED EMBODIMENTS

23 The present invention generally relates to a diffusional delivery system
24 suitable for the controlled and sustained release of a beneficial agent.

25 In one preferred embodiment, the system includes a reservoir comprising a
26 beneficial agent and a capillary channel in communication with the reservoir and the
27 exterior of the system for delivering the beneficial agent from the system. The
28 capillary channel has a cross-sectional area and a length selected to deliver the
29 beneficial agent at a predetermined rate. The system further includes an outer surface
30 that is impermeable and non-porous during delivery of the beneficial agent.

1 As used herein, the term "beneficial agent" refers to any composition or
2 substance that will produce a pharmacological or physiological response in a
3 mammalian organism. Such compositions and substances include drugs,
4 medicaments, vitamins, nutrients, and the like. The term "beneficial agent" also refers
5 to other compositions and substances that are delivered to other types of environments
6 such as pools, tanks, reservoirs, and the like. Included among these types of
7 compositions are biocides, sterilization agents, nutrients, vitamins, food supplements,
8 sex sterilants, fertility inhibitors, and fertility promoters.

9 The term "impermeable" refers to a material that is sufficiently impermeable to
10 environmental fluids as well as ingredients contained within the delivery system such
11 that the migration of such fluids and ingredients into or out of the system through the
12 impermeable material is so low as to have substantially no adverse impact on the
13 function of the system.

14 The term "non-porous" refers to a material that is essentially free of holes,
15 pores, or channels through which environmental fluids as well as ingredients
16 contained within the delivery system could traverse during delivery of the beneficial
17 agent.

18 In addition, as used herein, the term "capillary channel" refers to a generally
19 narrow, elongated passage through which ingredients inside the reservoir may move
20 outside of the delivery system and environmental fluids outside the system may move
21 inside to the reservoir. As will be explained hereinbelow, the capillary channel has a
22 length and cross-sectional area selected to delivery the beneficial agent from the
23 system at a desired rate by diffusion.

24 FIG. 1 illustrates one embodiment of the sustained release beneficial agent
25 delivery system of the present invention. While the system shown in FIG. 1 is
26 generally cylindrical, the system can be in any shape. The system comprises a
27 reservoir 5 containing a beneficial agent, an outer surface 10 that is impermeable
28 and non-porous, and a capillary channel 15 having a cross-sectional area and a length
29 selected to deliver the beneficial agent from reservoir 5 to an area outside of the
30 system at a predetermined rate. Capillary channel 15 contains an orifice 20 through

1 which the beneficial agent inside reservoir 5 exits the system as well as through which
2 environmental fluid outside of the system may enter reservoir 5.

3 FIG. 2 illustrates another embodiment of the sustained release beneficial agent
4 delivery system of the present invention. Again, while the system shown in FIG. 2 is
5 generally cylindrical, the system can be in any shape. The system similarly comprises
6 a reservoir 5' containing a beneficial agent, an outer surface 10' that is impermeable
7 and non-porous, and a capillary channel 15' having a cross-sectional area and a length
8 selected to deliver the beneficial agent from reservoir 5' to an area outside of the
9 system at a predetermined rate. Here, the capillary channel 15' has a helical
10 configuration. FIG. 2 further shows an orifice 20' in communication with capillary
11 channel 15' through which the beneficial agent inside reservoir 5' exits the system
12 as well as through which environmental fluid outside of the system may enter
13 reservoir 5'. FIG. 2 also shows an attachment 25 for affixing the system when it is
14 implanted into a mammalian subject. Attachment 25 is shown here in the form of a
15 ring. However, attachment 25 may be of any shape known in the art for affixing a
16 sustained release delivery system in an environment of use, e.g., for affixing an
17 implant inside a mammalian body or for affixing a device in a tank or other
18 environment of use.

19 The system according to the present invention has particular applicability in
20 providing a controlled and sustained release of beneficial agents effective in obtaining
21 a desired local or systemic physiological or pharmacological effect relating at least to
22 the following areas: treatment of cancerous primary tumors (e.g., glioblastoma);
23 chronic pain; arthritis; rheumatic conditions; hormonal deficiencies such as diabetes
24 and dwarfism; and modification of the immune response such as in the prevention of
25 transplant rejection and in cancer therapy. A wide variety of other disease states are
26 known by those of ordinary skill in the art, such as those described in Goodman and
27 Gilman, *The Pharmacological Basis of Therapeutics*, 8th ed., Pergamon Press, NY,
28 1990; and *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publ. Co., Easton,
29 PA, 1990; both of which are hereby incorporated by reference.

30 In addition to the above, the system is suitable for use in treating mammalian
31 organisms infected with AIDS and AIDS related opportunistic infections such as

1 cytomegalovirus infections, toxoplasmosis, pneumocystis carinii and mycobacterium
2 avium intercellular. For example, the system may be used to delivery a beneficial
3 agent effective in treating fungal infection in the mouth of AIDS patients. If such a
4 use is desired, the system may be designed to have a shape suitable for implanting
5 into a tooth of the patient.

6 The system is particularly useful for treating ocular conditions such as
7 glaucoma, proliferative vitreoretinopathy, diabetic retinopathy, uveitis, and keratitis.
8 The system is also particularly useful as an ocular system in treating mammalian
9 organisms suffering from cytomegalovirus retinitis wherein the system is surgically
10 implanted within the vitreous of the eye.

11 Suitable classes of beneficial agents for use in the system of the present
12 invention include, but are not limited to the following:

- 13 1. Peptides and proteins such as cyclosporin, insulin, growth hormones,
14 insulin related growth factor, heat shock proteins and related compounds;
- 15 2. Anesthetics and pain killing agents such as lidocaine and related
16 compounds, and benzodiazepam and related compounds;
- 17 3. Anti-cancer agents such as 5-fluorouracil, adriamycin and related
18 compounds;
- 19 4. Anti-inflammatory agents such as 6-mannose phosphate;
- 20 5. Anti-fungal agents such as fluconazole and related compounds;
- 21 6. Anti-viral agents such as trisodium phosphomonoformate,
22 trifluorothymidine, acyclovir, cidofovir, ganciclovir, DDI and AZT;
- 23 7. Cell transport/mobility impeding agents such as colchicine,
24 vincristine, cytochalasin B and related compounds;
- 25 8. Anti-glaucoma drugs such as beta-blockers: timolol, betaxolol atenolol,
26 etc.;
- 27 9. Immunological response modifiers such as muramyl dipeptide and
28 related compounds;
- 29 10. Steroidal compounds such as dexamethasone, prednisolone and related
30 compounds; and
- 31 11. Carbonic anhydrase inhibitors.

1 In addition to the above agents, other beneficial agents which are suitable for
2 administration, especially to the eye and its surrounding tissues, to produce a local or
3 a systemic physiologic or pharmacologic effect can be used in the system of the
4 present invention. Examples of such agents include antibiotics such as tetracycline,
5 chlortetracycline, bacitracin, neomycin, polymyxin, gramicidin, oxytetracycline,
6 chloramphenicol, gentamycin, and erythromycin; antibacterials such as sulfonamides,
7 sulfacetamide, sulfamethizole and sulfisoxazole; antivirals such as idoxuridine; and
8 other antibacterial agents such as nitrofurazone and sodium propionate; antiallergenics
9 such as antazoline, methapyrilene, chlorpheniramine, pyrilamine, and
10 propenpyridamine; anti-inflammatories such as hydrocortisone, hydrocortisone
11 acetate, dexamethasone 21-phosphate, fluocinolone, medrysone, methylprednisolone,
12 prednisolone 21-phosphate, prednisolone acetate, fluoromethalone, betamethasone,
13 and triminolone; decongestants such as phenylephrine, naphazoline, and
14 tetrahydrazoline; miotics and anti-cholinesterases such as pilocarpine, eserine
15 salicylate, carbachol, di-isopropyl fluorophosphate, phospholine iodine, and
16 demecarium bromide; mydriatics such as atropine sulfate, cyclopentolate,
17 homatropine, scopolamine, tropicamide, eucatropine, and hydroxyamphetamine;
18 and sympathomimetics such as epinephrine.

19 Any pharmaceutically acceptable form of the aforementioned beneficial
20 agents may be employed in the practice of the present invention, e.g., the free base or
21 a pharmaceutically acceptable salt or ester thereof. Pharmaceutically acceptable salts,
22 for instance, include sulfate, lactate, acetate, stearate, hydrochloride, tartrate, maleate
23 and the like. Beneficial agents which are water soluble are particularly useful in the
24 present invention.

25 The beneficial agents may also be used in combination with pharmaceutically
26 acceptable carriers and, optionally, additional ingredients such as antioxidants,
27 stabilizing agents, diffusion enhancers, and the like. For example, where water
28 uptake by the beneficial agent is undesired, the beneficial agent can be formulated
29 in a hydrophobic carrier, such as a wax or an oil, that would allow sufficient diffusion
30 of the beneficial agent from the system.

1 In a preferred embodiment, the beneficial agents, e.g., proteins, may be
2 formulated in a glassy matrix of sugar which tends to protect the beneficial agent from
3 hydrolytic degradation.

4 A large number of materials can be used to construct the system of the present
5 invention. The only requirements are that they are suitably inert and are impermeable
6 and non-porous as defined hereinabove. When the system according to the present
7 invention is used in the body, the material selected should also be biocompatible.
8 Materials that are suitable for fabricating the present invention include naturally
9 occurring or synthetic materials, especially those, that are biologically compatible
10 with body fluids and eye tissues, and essentially insoluble over an extended period of
11 time in the fluids with which the material will come into contact. The use of rapidly
12 dissolving materials, materials that are highly soluble in eye fluids, or materials that
13 develop pores, holes, or channels during delivery of the beneficial agent are to be
14 avoided since dissolution or break down of the outer surface of the system would
15 affect the constancy of the controlled release of the beneficial agent as well as the
16 capability of the system to remain in place for a prolonged period of time.

17 Naturally occurring or synthetic materials that are biologically compatible
18 with body fluids and eye tissues suitable for use in the present invention generally
19 include metals, ceramics, glass, polymers, and combinations thereof. Examples
20 of such polymeric materials include polyethylene, polypropylene, polyethylene
21 terephthalate, plasticized polyvinyl chloride, crosslinked polyester, polycarbonate,
22 polysulfone, polystyrene, poly(2-pentene), poly(methylmethacrylate), poly(1,4-
23 phenylene), polytetrafluoroethylene, and poly-ethylene-vinylacetate (EVA).
24 Preferred polymers include polyethylene and polypropylene. Preferred polymers may
25 be chosen according to their biocompatibility, degree of impermeability, transparency
26 to light, or ability to be detected by external measurement such as ultrasound or x-ray.

27 Preferably, the polymer is also bioerodible. Suitable bioerodible polymers
28 include poly(glycolic acid), poly(lactic acid), copolymers of lactic/glycolic acid,
29 polyorthoesters, polyanhydrides, polyphosphazones, and polycaprolactone. These
30 polymers are particularly preferred because of their slow erosion properties and
31 should not undergo undue changes during the course of the beneficial agent delivery.

1 Exemplary metals suitable for use in the present invention include titanium,
2 stainless steel, tin, and aluminum. Preferably, the metal is titanium or a titanium
3 alloy.

4 The outer surface of the system as well as the capillary channel may be made
5 of any of the above-listed materials or combinations thereof. The outer surface and
6 the capillary channel can be constructed of the same or different material. For
7 example, the outer surface material of the system can be a metal while the material
8 defining the capillary channel can be a polymer.

9 The system according to the present invention may be made in a variety
10 of ways. For example, if the system is going to be made entirely of a polymer,
11 then the polymer can be injection molded or die cast into a desired shape and size.
12 An effective amount of the beneficial agent is then obtained, for example, in an
13 aqueous solution formulation. The beneficial agent can be filled into the reservoir
14 and into the capillary channel by any conventional means such as a syringe or a
15 pipette. Care should be taken in filling the system with the beneficial agent so as to
16 avoid any air pockets in the reservoir or the capillary channel because the air pocket
17 could act as a lock, preventing wetting and/or migration of the beneficial agent to the
18 desired location outside of the system. Thus, in this embodiment, at the very least,
19 the capillary channel should be filled with a medium that draws water into the
20 reservoir. This medium could be water itself, an aqueous solution of the beneficial
21 agent, or any biocompatible water attracting agent initially present as a solid.

22 The above description of how to make the system of the present invention is
23 merely illustrative and should not be considered as limiting the scope of the invention
24 in any way, as various methods for making the system would be readily apparent to
25 one skilled in the art. In particular, the methods of making the system depend on the
26 identity of the beneficial agent as well as the outer surface material. Given the
27 beneficial agent and material selected, one skilled in the art could easily make the
28 system of the present invention using conventional fabrication techniques.

1 Naturally, the system according to the present invention can be manufactured
2 to hold any quantity of the beneficial agent desired. The cross-sectional area and the
3 length of the capillary channel can also be varied to obtain the desired rate of delivery
4 as more fully explained below.

5 The system according to the present invention is a diffusional beneficial agent
6 delivery system in which control over the diffusion of the beneficial agent is exerted
7 by the capillary channel.

8 Mathematically, a diffusional process can be described by Fick's Law:

9
10
$$J = -D \cdot A \cdot (\Delta C / \ell)$$

11
12 in which J is the mass transport of the beneficial agent from the system, D is the
13 diffusivity of the beneficial agent, A is the surface area through which the diffusion
14 takes place, ΔC is the concentration difference of the beneficial agent inside and
15 outside of the delivery system, and ℓ is the length of the diffusional path.

16 In prior art systems, the primary method for controlling the mass transport J
17 of a beneficial agent from a reservoir containing the agent is to surround the reservoir
18 with a membrane through which the beneficial agent has a relatively low diffusivity
19 D. Adjustments in the surface area A and thickness ℓ of the membrane can then be
20 made to obtain the desired mass transport.

21 In direct contrast to the prior art systems, it is particularly preferred that the
22 system according to the present invention does not contain a permeable or
23 semipermeable membrane through which the beneficial agent or environmental fluid
24 must pass in order for the beneficial agent to be delivered. Thus, in the present
25 invention, the rate of delivery of the beneficial agent is not controlled by the
26 beneficial agent's diffusivity through the material surrounding the reservoir. Instead,
27 it is controlled by selecting the surface area A (i.e., the cross-sectional area of the
28 capillary channel) and the diffusional path length ℓ (i.e., the length of the capillary
29 channel) through which the diffusion takes place. The smaller the value of A and the
30 larger the value of ℓ , the lower the mass transport will be.

1 For any desired rate of delivery, the particular cross-sectional area A and
2 length ℓ of the capillary channel can be determined based on Fick's Law above. It is
3 within the level of one skilled in the art to determine the cross-sectional area A and
4 length ℓ of the capillary channel once the diffusivity D of the beneficial agent, the
5 mass transport J , and the difference in concentration ΔC of the beneficial agent from
6 inside to outside of the system are known. Generally, the diffusivity D of a particular
7 beneficial agent (e.g., drugs) through a particular medium can be calculated
8 experimentally or by consulting standard handbooks or review articles known to
9 those skilled in the art. See, e.g., *Remington's*, pp. 1680-81; and R.W. Baker & H.K.
10 Lonsdale, *Controlled Release: Mechanisms and Rates* in ADVANCES IN
11 EXPERIMENTAL MEDICINE AND BIOLOGY, Vol. 47, pp. 15-71 (Tanquary & Lacey
12 eds., 1974), the contents of which are incorporated by reference.

13 The mass transport J , in the case where the beneficial agent is a drug, is
14 selected based on the effective dosage of the drug. Typical dosages of drugs for
15 particular ailments may be found in standard medical handbooks. See, e.g., Goodman
16 & Gilman; *Physician's Desk Reference* (PDR); and *The Extra Pharmacopeia* (Royal
17 Pharm. Soc.). The difference in concentration ΔC can be determined easily based
18 on the concentration of the beneficial agent inside the reservoir of the system, which
19 is usually known, and the concentration of the same beneficial agent outside the
20 system, which is typically about zero, but may be greater than zero depending on the
21 specific beneficial agent. Once the values of J , D , and ΔC have been ascertained,
22 then Fick's Law may be used to determine acceptable values for A and ℓ which would
23 then define the cross-sectional area and length required for the capillary channel.

24 As is readily apparent, the method of mass transport control according to the
25 present invention is fundamentally different from the use of a permeable membrane.
26 One important advantage in using such a method to control the mass transport is that
27 the system of the present invention can be used to deliver hydrophilic molecules,
28 which are notoriously difficult to deliver from a membrane controlled diffusional
29 system.

1 It is also important to note that the method of delivery of the present invention
2 is not the same as restricting the flow of a liquid by using a narrow orifice. In fact,
3 preferably, there is no viscous flow of liquid through the capillary channel of the
4 system. In this preferred embodiment, the capillary channel is filled with a loosely
5 crosslinked, highly swollen, but immobilized gel through which diffusion of the
6 beneficial agent can take place. Such gels include swollen polyacrylates,
7 polymethacrylates, crosslinked gelatins, crosslinked carbohydrates such as NaCMC,
8 HPMC and HPC, alginates, aluminum stearate gels, and PVP gels.

9 Another advantage of the system according to the present invention is that
10 there are no moving parts and, thus, it would be easier to fabricate than plunger-type
11 osmotic delivery systems known in the art.

12 As noted above, the system according to the present invention could be
13 employed to treat a mammalian organism to obtain a desired local or systemic
14 physiological or pharmacological effect. The system could be employed by
15 administering the sustained release beneficial agent delivery system to the mammalian
16 organism and allowing the beneficial agent therein to pass out of the system to come
17 in direct contact with the mammalian organism.

18 The beneficial agent delivery system of the present invention may be
19 administered to a mammalian organism via any route of administration known
20 in the art. Such routes of administration include intraocular, oral, subcutaneous,
21 intramuscular, intraperitoneal, intranasal, dermal, intrathecal, and the like.
22 In addition, one or more of the systems may be administered at one time or
23 more than one agent may be included in the reservoir or inner core.

24 The beneficial agent delivery system of the present invention is particularly
25 suitable for direct implantation into the vitreous humor of the eye and for application
26 to an intraocular lens.

27 These methods of administration and techniques for their preparation are well
28 known by those of ordinary skill in the art. Techniques for their preparation are set
29 forth, for example, in *Remington's Pharmaceutical Sciences*.

1 The beneficial agent delivery system may be administered at a suitable
2 location for a sufficient period of time and under conditions which allow treatment of
3 the disease state of concern.

4 For localized beneficial agent delivery, the system of the present invention
5 may be surgically implanted at or near the site of action. This is the case when it is
6 used in treating ocular conditions, primary tumors, rheumatic and arthritic conditions,
7 and chronic pain.

8 For systemic relief, the system may be implanted subcutaneously,
9 intramuscularly or intraperitoneally. This is the case when the system is to give
10 sustained systemic levels and avoid premature metabolism.

11 In one particularly preferred embodiment of the invention, an intra-ocular
12 implant system containing cidofovir as the beneficial agent in an effective amount to
13 treat AIDS induced cytomegalovirus retinitis infection of the eye may be prepared.
14 It has been estimated that cidofovir would be effective in treating this disease at
15 dosages of 0.5 to 2 $\mu\text{g}/\text{day}$ when delivered directly into the vitreous humor. Cidofovir
16 has three ionizable sites and, thus, is not expected to diffuse readily through polymeric
17 membranes. It is highly soluble ($> 150 \text{ mg}/\text{ml}$) in water and is extremely stable in
18 aqueous solution. Thus, it is very suitable for use in the system according to the
19 present invention.

20 In this embodiment, the reservoir of the system and the capillary channel
21 would be filled with a saturated aqueous solution of cidofovir. Assuming that the
22 diffusivity D of cidofovir in water is $1 \times 10^{-6} \text{ cm}^2/\text{s}$ and its solubility ΔC in water is
23 $150 \text{ mg}/\text{ml}$, then a desired dosage of $1 \mu\text{g}/\text{day}$ can be obtained with a capillary
24 channel having a length of 1 cm and a diameter of 0.1 mm. If the reservoir is initially
25 filled with at least about 730 μg of cidofovir, then the system could deliver cidofovir
26 for two years or longer. Such a system may remain in the vitreous humor
27 permanently after treatment is complete.

28 Generally, the amount of beneficial agent used in the system of the present
29 invention ranges from about 0.01 mg to about 2.5 g. Preferably, the system contains
30 from about 1 mg to about 100 mg of the beneficial agent. Most preferably, the system
31 contains from about 1 mg to about 10 mg of the beneficial agent. These preferred

1 ranges may provide sustained release of the beneficial agent for a period of from
2 several days to over one year.

3 Preferably, the capillary channel of the system according to the present
4 invention has a substantially circular cross-sectional area. In which case, the capillary
5 channel preferably has a diameter of about 0.01 mm to about 1 mm, and a length of
6 about 0.1 cm to about 25 cm. The system as a whole preferably has a diameter of
7 about 0.1 mm to about 10 mm, and a length of about 1 mm to about 50 mm. When
8 such a system is prepared for implantation within the vitreous of the eye, it is
9 preferred that the system does not exceed about 5 mm in any direction. Thus, the
10 cylindrical system shown in FIGS. 1 and 2 would preferably not exceed 5 mm in
11 length or diameter.

12 In a separate preferred embodiment, the system according to the present
13 invention includes a reservoir comprising a beneficial agent formulated in a glassy
14 sugar matrix and a capillary channel communicating between the reservoir and
15 the exterior of the system for delivering the beneficial agent from the system.
16 The capillary channel has a cross-sectional area and a length selected to deliver
17 the beneficial agent at a predetermined rate.

18 Here, there is no requirement that the outer surface of the system be
19 impermeable and non-porous during delivery of the beneficial agent as in the first
20 embodiment described above. However, it is contemplated by the present invention
21 that the outer surface of the system in this embodiment could be impermeable and
22 non-porous during delivery of the beneficial agent.

23 Preferably, the beneficial agent employed in this system is a peptide or protein
24 such as those mentioned hereinabove.

25 It has recently been suggested that beneficial agents, particularly proteins,
26 formulated in glass matrices may extend their shelf life and eliminate the need for
27 cold storage. See, e.g., F. Franks, *Long-Term Stabilization of Biologicals*,
28 *BIO/TECHNOLOGY*, Vol. 12, pp. 253-56 (Mar. 1994); the contents of which are hereby
29 incorporated by reference.

1 Proteins may be formulated in a glass matrix by removing water from a
2 homogeneous solution thereof. The water can be removed either by evaporation or
3 by rapidly cold quenching the solution. This process is commonly referred to as
4 vitrification. As water is removed from the solution, it becomes increasingly viscous
5 until a "solidified" liquid containing the proteins is obtained. The "solidified" liquid
6 is generically called glass.

7 Glasses have a number of unique physical and chemical properties which
8 make them ideal for beneficial agent formulation. Among them, the most important is
9 that the solidified liquid retains the molecular disorder of the original solution. This
10 disorder contributes to the glasses' long-term stability by preventing crystallization
11 and chemical reactions of the proteins encased therein.

12 Sugars can also play an important part in stabilizing protein formulations.
13 In solution, they are known to shift the denaturation equilibrium of proteins toward
14 the native state. Most sugars, particularly low molecular weight carbohydrates, are
15 also known to vitrify easily and to provide a glassy matrix that retards inactivating
16 reactions of the proteins.

17 For illustrative purposes, the glassy sugar matrix for use in the system
18 according to the present invention can be made by compressing a lyophilized mix of a
19 protein with a sugar and a buffer, and optionally, binders. The protein-sugar matrix
20 should be incorporated into the system with minimal inclusion of air. Various ways
21 are known in the art for such incorporation. Preferably, upon vitrification, the
22 formulation chosen will have a glass transition temperature (T_g) above the
23 environmental temperature. The T_g of a formulation is a function of the relative
24 amounts of the formulation components, and its determination is known to those
25 skilled in the art.

26 Alternatively, the protein may be vitrified or encased in the glassy sugar
27 matrix directly in the reservoir of the delivery system.

28 Examples of proteins and proteinaceous compounds which may be formulated
29 and employed in the delivery system according to the present invention include those
30 proteins which have biological activity or which may be used to treat a disease or
31 other pathological condition. They include, but are not limited to growth hormone,

1 Factor VIII, Factor IX and other coagulation factors, chymotrypsin, trypsinogen, alpha-
2 interferon, beta-galactosidase, lactate dehydrogenase, growth factors, clotting factors,
3 enzymes, immune response stimulators, cytokines, lymphokines, interferons,
4 immunoglobulins, retroviruses, interleukins, peptides, somatostatin, somatotropin
5 analogues, somatomedin-C, Gonadotropic releasing hormone, follicle stimulating
6 hormone, luteinizing hormone, LHRH, LHRH analogues such as leuprolide, nafarelin
7 and goserelin, LHRH agonists and antagonists, growth hormone releasing factor,
8 calcitonin, colchicine, gonadotropins such as chorionic gonadotropin, oxytocin,
9 octreotide, somatotropin plus an amino acid, vasopressin, adrenocorticotrophic
10 hormone, epidermal growth factor, prolactin, somatotropin plus a protein,
11 cosyntropin, lypressin, polypeptides such as thyrotropin releasing hormone, thyroid
12 stimulation hormone, secretin, pancreozymin, enkephalin, glucagon, endocrine agents
13 secreted internally and distributed by way of the bloodstream, and the like. Other
14 agents which may be encased and delivered include α_1 antitrypsin, insulin and other
15 peptide hormones, adrenal cortical stimulating hormone, thyroid stimulating hormone,
16 and other pituitary hormones, interferon α , β and δ , erythropoietin, growth factors
17 such as GCSF, GM-CSF, insulin-like growth factor 1, tissue plasminogen activator,
18 CF4, dDAVP, tumor necrosis factor receptor, pancreatic enzymes, lactase,
19 interleukin-1 receptor antagonist, interleukin-2, tumor suppresser proteins, cytotoxic
20 proteins, viruses, viral proteins, recombinant antibodies and antibody fragments and
21 the like. Analogs, derivatives, antagonists, agonists, and pharmaceutically acceptable
22 salts of the above may also be used.

23 The above agents are useful for the treatment or prevention of a variety of
24 conditions including, but not limited to hemophilia and other blood disorders,
25 growth disorders, diabetes, leukemia, hepatitis, renal failure, HIV infection, hereditary
26 diseases such as cerebrosidase deficiency and adenosine deaminase deficiency,
27 hypertension, septic shock, autoimmune diseases such as multiple sclerosis, Graves
28 disease, systemic lupus erythematosus and rheumatoid arthritis, shock and wasting
29 disorders, cystic fibrosis, lactose intolerance, Crohn's disease, inflammatory bowel
30 disease, gastrointestinal and other cancers.

1 The protein compounds useful in the formulations of the present invention can
2 be used in the form of a salt, preferably a pharmaceutically acceptable salt. Useful
3 salts are known to those skilled in the art and include salts with inorganic acids,
4 organic acids, inorganic bases, or organic bases.

5 Sugars useful for preparing the glassy matrix include, but are not limited to
6 glucose, sucrose, trehalose, lactose, maltose, raffinose, stachyose, maltodextrins,
7 cyclodextrins, sugar polymers such as dextrans and their derivatives, ficoll, and
8 starch.

9 Buffers useful for formulating the glassy matrix include, but are not limited
10 to MES, HEPES, citrate, lactate, acetate, and amino acid buffers.

11 Preferably, the system comprising the glassy sugar matrix is constructed
12 of a bioerodible polymer with a low water permeability. Such polymers include
13 poly(glycolic acid), poly(lactic acid), copolymers of lactic/glycolic acid,
14 polyorthoesters, polyanhydrides, polyphosphazones, polycaprolactone. These
15 polymers are particularly preferred because of their slow erosion properties and
16 low water uptake; thus, they should not undergo undue changes during the course
17 of the beneficial agent delivery.

18 In operation, the osmotically active glassy sugar protein matrix may absorb
19 some water through the polymer material. However, with the proper selection of
20 polymer material, water uptake through the polymer wall can be minimized. Thus,
21 the capillary channel would be the predominant route of mass transport as well as the
22 primary method for controlling the rate of delivery of the protein. Specifically, the
23 rate at which the glassy sugar protein matrix dissolves is determined primarily by the
24 rate of water uptake through the capillary channel and the rate of release of the sugar.
25 As in the first embodiment, the rate of protein released from the system in this
26 embodiment is determined by its diffusion through the capillary channel. Again,
27 for a given concentration of protein, this rate can be adjusted by changing the length
28 and the cross-sectional area of the capillary channel.

Simply put, the dimensions of the capillary channel control the amount of water that is drawn into the reservoir and, thus, control the rate at which the sugar matrix dissolves. At the same time, the dimensions of the capillary channel control the rate of delivery of the protein from the system.

5 An advantage of this embodiment of the invention is that as long as the protein
6 is inside the delivery system, it is protected either by the glassy sugar matrix or by the
7 presence of the dissolved stabilizer molecules that once formed the sugar matrix.
8 Thus, by using the system according to the present invention, it is possible to obtain a
9 sustained and controlled release of a protein that retains more biological activity than
10 conventional formulations.

11 The system according to this embodiment of the invention can be made and
12 used in the same manner as the system of the first embodiment described above.

13 The following example is merely illustrative of the present invention and
14 should not be considered as limiting the scope of the invention, as the example and
15 other equivalents thereof will become more apparent to those skilled in the art in light
16 of the present disclosure.

EXAMPLE

Four cylindrical cups, labeled A, B, C, and D, were provided as the reservoir. The cups were made of acrylate, and had a length of 2 cm, an outside diameter of 8 mm, and an inside diameter of 4 mm. The cups were left open at one end for filling with the beneficial agent. An enlarged view of the delivery system of this Example can be seen in FIG. 3.

A slurry of bupivacaine hydrochloride in a saturated aqueous solution thereof was provided as the beneficial agent. The cups 30 were all filled with enough of the slurry such that, after settling, they all contained a layer of solid drug 35 of about 1 cm thick and a layer of saturated solution of drug 40 on top of the solid layer. No attempt was made to quantify the amount of drug in the cups in any other way.

A diffusion controller 45 containing a capillary channel 15" was then inserted into the open end of each of the cups. The diffusion controller 45 was made of acrylate and had a cylindrical shape. The diffusion controller 45 had a length of

1 5 mm and a diameter of about 4 mm. A 1 mm orifice was drilled into each of the
2 diffusion controllers in the axial direction to provide the capillary channel 15".

3 Great care had to be taken to remove air from the cups because initial
4 experiments were repeatedly hampered by small air bubbles blocking the capillary
5 channel in the diffusion controller. It is believed that the best way to remove the
6 small air bubbles is to fill the cups with a de-aerated slurry of the drug, and then
7 draw a vacuum on the cups several times before capping them with the diffusion
8 controllers.

9 Each of the cups 30 was then glued in a vertical position to the bottom of a
10 scintillation vial. The vials were filled with 15 ml of water, which was replaced at
11 regular intervals and measured for drug content. The vials were shaken at 37° C in a
12 Dubnoff type water bath. The experiment was continued until most of the cups no
13 longer contained visible amounts of solid drug.

14 The release rates of each of the delivery systems A, B, C, and D are
15 graphically shown in FIG. 4 as a function of time. As seen in FIG. 4, each of the
16 delivery systems released the drug at a relatively constant and reproducible rate.
17 In particular, although the systems show a slight burst of drug release at day 1,
18 from day 2 through day 23 the delivery rates were relatively constant. At day 24,
19 the effects of drug depletion became evident in system D. The average release rates
20 of the four systems range from 835 mcg/day at day 2 to 530 mcg/day at day 23.

21 The results of this example demonstrate that it is possible to achieve relatively
22 constant release rates over a substantial period of time by using a diffusional delivery
23 system according to the present invention.

24 While the invention has been described and illustrated with reference to certain
25 preferred embodiments thereof, those skilled in the art will appreciate that various
26 modifications, changes, omissions, and substitutions can be made without departing
27 from the spirit and scope of the invention. As such, these changes and/or
28 modifications are properly and equitably intended to be within the full range of
29 equivalence of the following claims.

1 Claims:

- 2 1. A sustained release delivery system for delivering a beneficial agent at
3 a predetermined rate comprising:
4 (a) a reservoir comprising said beneficial agent;
5 (b) a capillary channel in communication with said reservoir and the
6 exterior of the system for delivering said beneficial agent from the system; and
7 (c) an outer surface that is impermeable and non-porous during delivery of
8 the beneficial agent,
9 said capillary channel having a cross-sectional area and a length selected to
10 provide said predetermined rate.
- 11 2. The system according to claim 1, wherein said beneficial agent is
12 cidofovir.
- 13 3. The system according to claim 1, wherein said beneficial agent is a
14 protein or peptide.
- 15 4. The system according to claim 3, wherein said protein is occluded in a
16 glassy sugar matrix.
- 17 5. The system according to claim 1, wherein said capillary channel is
18 filled with said beneficial agent.
- 19 6. The system according to claim 1, wherein said capillary channel is
20 filled with an immobilized gel capable of diffusing said beneficial agent from said
21 reservoir to the exterior of the system.
- 22 7. The system according to claim 1, wherein said capillary channel is
23 filled with water.
- 24 8. The system according to claim 1, wherein said outer surface is selected
25 from the group consisting of metals, ceramics, glass, and polymers.
- 26 9. The system according to claim 8, wherein said outer surface is a
27 bioerodible polymer.
- 28 10. The system according to claim 9, wherein said bioerodible polymer is
29 selected from the group consisting of poly(glycolic acid), poly(lactic acid),
30 copolymers of lactic/glycolic acid, polyorthoesters, polyanhydrides,
31 polyphosphazones, and polycaprolactones.

- 1 11. The system according to claim 8, wherein said non-porous material is
2 titanium or a titanium alloy.
- 3 12. The system according to claim 1, wherein said capillary channel is
4 helical.
- 5 13. The system according to claim 1, wherein said system is capable of
6 being implanted into a mammalian organism.
- 7 14. The system according to claim 13, further comprising a ring at one end
8 thereof for affixing said system inside said mammalian organism.
- 9 15. The system according to claim 1, wherein said system is capable of
10 continuously delivering from about 0.5 to about 2 $\mu\text{g/day}$ of said beneficial agent.
- 11 16. The system according to claim 1, wherein said system is capable of
12 continuously delivering said beneficial agent over a period of at least two years.
- 13 17. The system according to claim 1, wherein said capillary channel has a
14 diameter of about 0.01 mm to about 1 mm.
- 15 18. The system according to claim 1, wherein said capillary channel has a
16 length of about 0.1 cm to about 25 cm.
- 17 19. The system according to claim 1, having a cylindrical shape.
- 18 20. The system according to claim 19, having a diameter of about 0.1 mm
19 to about 10 mm, and a length of about 1 mm to about 50 mm.
- 20 21. A sustained release delivery system for delivering a beneficial agent
21 formulated in a glassy sugar matrix at a predetermined rate comprising:
- 22 (a) a reservoir comprising said beneficial agent; and
- 23 (b) a capillary channel in communication with said reservoir and the
24 exterior of the system for delivering said beneficial agent from the system,
25 said capillary channel having a cross-sectional area and a length selected to
26 provide said predetermined rate.
- 27 22. The system according to claim 21, wherein said beneficial agent is a
28 protein or peptide.
- 29 23. The system according to claim 22, wherein said system is made of a
30 bioerodible polymer.

1 24. The system according to claim 23, wherein said bioerodible polymer is
2 selected from the group consisting of poly(glycolic acid), poly(lactic acid),
3 copolymers of lactic/glycolic acid, polyorthoesters, polyanhydrides,
4 polyphosphazones, and polycaprolactones.

5 25. A method of delivering a beneficial agent at a predetermined rate, said
6 method comprising positioning a sustained release delivery system at a location in
7 need of such beneficial agent, said sustained release delivery system comprising:

- 8 (a) a reservoir comprising said beneficial agent;
9 (b) a capillary channel in communication with said reservoir and the
10 exterior of the system for delivering said beneficial agent from the system; and
11 (c) an outer surface that is impermeable and non-porous during delivery of
12 the beneficial agent,

13 said capillary channel having a cross-sectional area and a length selected to
14 provide said predetermined rate.

15 26. A method of delivering a beneficial agent formulated in a glassy sugar
16 matrix at a predetermined rate, said method comprising positioning a sustained release
17 delivery system at a location in need of such beneficial agent, said sustained release
18 delivery system comprising:

- 19 (a) a reservoir comprising said beneficial agent; and
20 (b) a capillary channel in communication with said reservoir and the
21 exterior of the system for delivering said beneficial agent from the system,

22 said capillary channel having a cross-sectional area and a length selected to
23 provide said predetermined rate.

24 27. A method of preparing a sustained release delivery system for
25 delivering a beneficial agent at a predetermined rate, said method comprising the steps
26 of:

- 27 (a) providing a reservoir having an outer surface that is impermeable and
28 non-porous during delivery of the beneficial agent;

29 (b) filling said reservoir with the beneficial agent; and

- 1 (c) providing the reservoir with a diffusion controller,
2 said diffusion controller comprising a capillary channel having a cross-
3 sectional area and a length selected to provide said predetermined rate.
- 4 28. A method of preparing a sustained release delivery system for
5 delivering a beneficial agent formulated in a glassy sugar matrix at a predetermined
6 rate, said method comprising the steps of:
- 7 (a) providing a reservoir;
8 (b) providing a beneficial agent formulated in a glassy sugar matrix in said
9 reservoir; and
- 10 (c) providing the reservoir with a diffusion controller,
11 said diffusion controller comprising a capillary channel having a cross-
12 sectional area and a length selected to provide said predetermined rate.

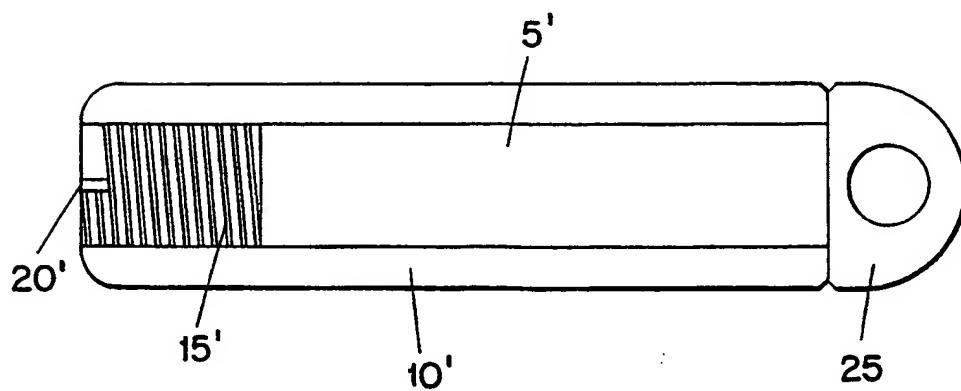
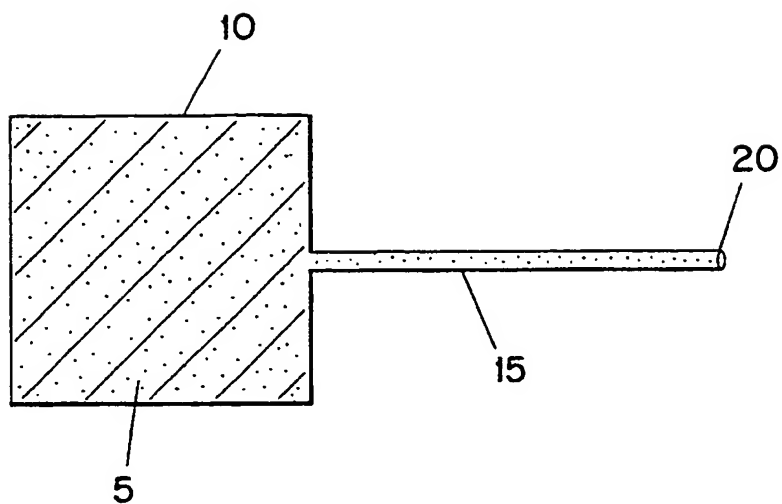
FIG. 1*FIG. 2*

FIG. 3

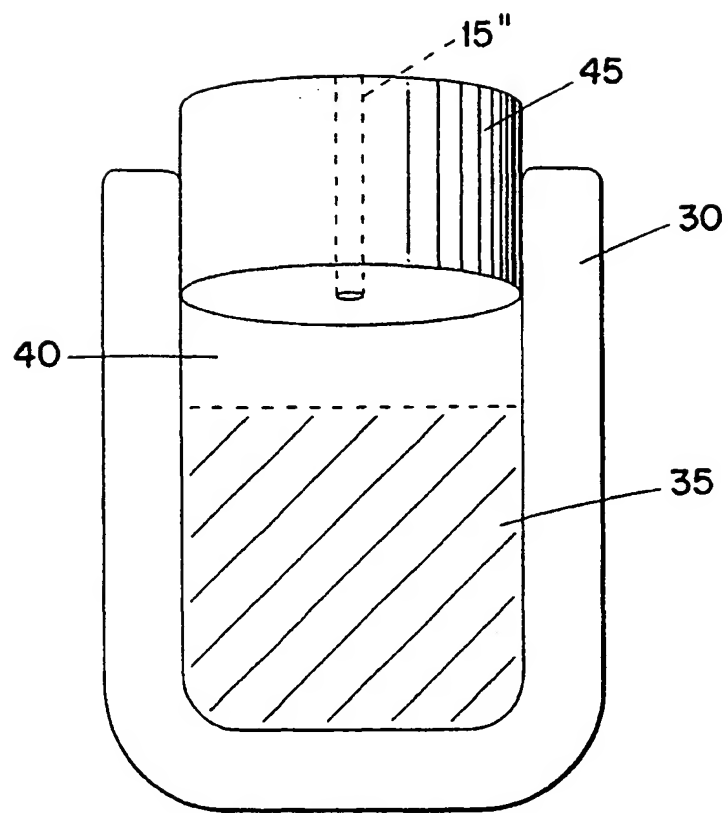
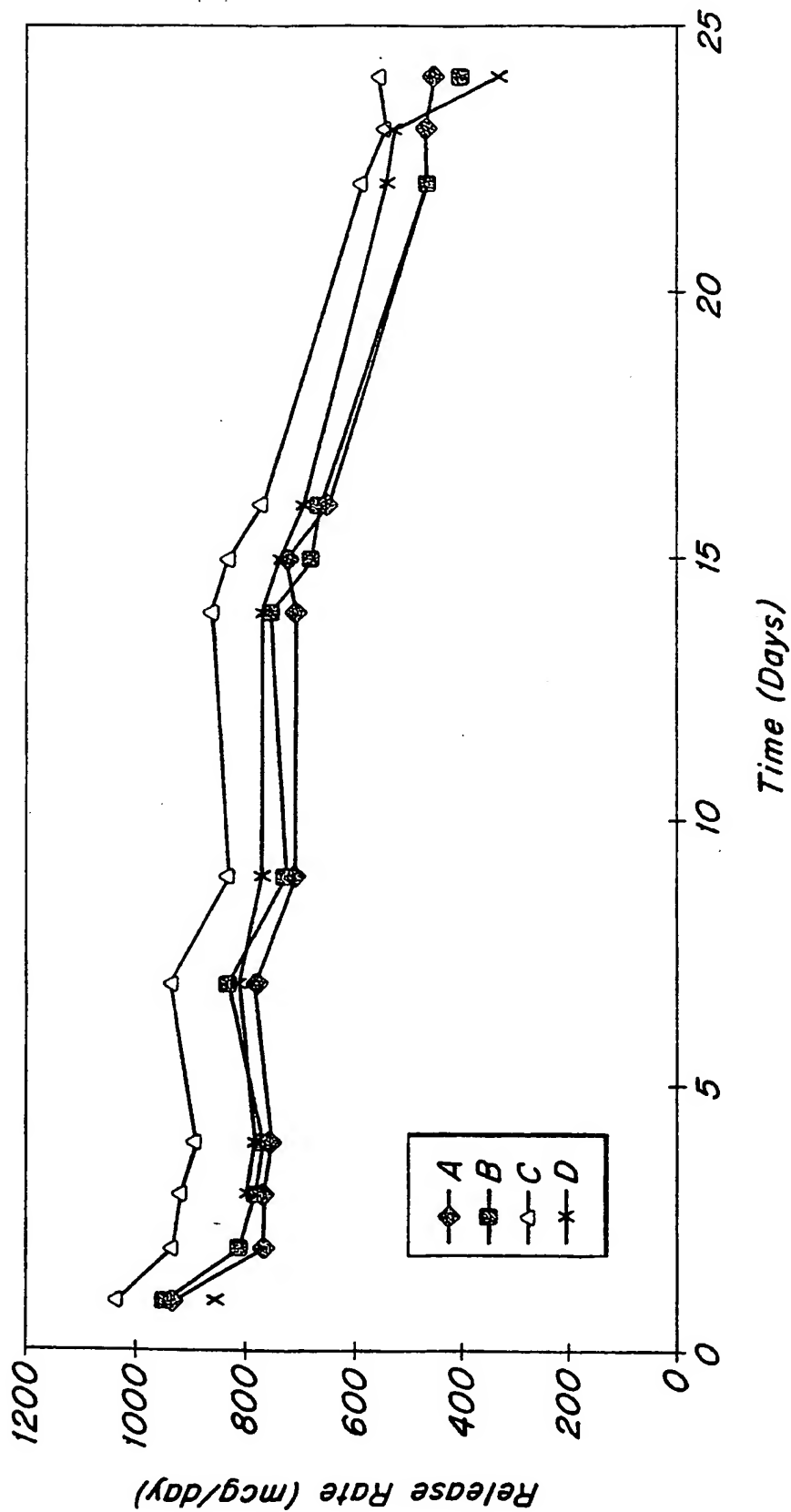


FIG. 4
ORIFICE CONTROLLED RELEASE RATES



INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/05138

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 3 845 770 A (FELIX THEEUWES) 5 November 1974 see the whole document ---	1-28
A	US 3 760 984 A (FELIX THEEUWES) 25 September 1973 see the whole document -----	1-28

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

5 June 1998

Date of mailing of the international search report

16/06/1998

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Ventura Amat, A

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int lonal Application No

PCT/US 98/05138

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3845770 A	05-11-1974	AR 199301 A	23-08-1974
		AT 332563 B	11-10-1976
		AU 466503 B	30-10-1975
		AU 5640773 A	05-12-1974
		BE 800485 A	01-10-1973
		CA 1028212 A	21-03-1978
		CH 578464 A	13-08-1976
		DE 2328409 A	20-12-1973
		DK 134922 B	14-02-1977
		FR 2188568 A	18-01-1974
		GB 1415210 A	26-11-1975
		JP 1230864 C	26-09-1984
		JP 49061325 A	14-06-1974
		JP 59006843 B	15-02-1984
		NL 7307699 A,B,	07-12-1973
		SE 402532 B	10-07-1978
		ZA 7303734 A	26-06-1974
US 3760984 A	25-09-1973	NONE	